(2)

AD_____

Phase I Clinical Pharmacology Studies

ANNUAL REPORT

Paul S. Lietman, M.D., Ph.D.
Brent G. Petty, M.D.
David M. Kornhauser, M.D.

April 21, 1989

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Maryland 21701-5012

Contract No. DAMD17-85-C-5133

Division of Clinical Pharmacology
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

1a REPORT SECURITY CLASSIFICATION Unclassified	1b RESTRICTIVE MARKINGS
2a SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b DECLASSIFICATION/DOWNGRADING SCHEDULE	
4 PERFORMING ORGANIZATION REPORT NUMBER(S)	5 MONITORING ORGANIZATION REPORT NUMBER(S)
6a NAME OF PERFORMING ORGANIZATION The Johns Hopkins University School of Medicine 6b OFFICE SYMBOL (If applicable)	7a NAME OF MONITORING ORGANIZATION
6c ADDRESS (City, State, and ZIP Code) 600 North Wolfe Street Baltimore, Maryland 21205	7b ADDRESS (City, State, and ZIP Code)
8a NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command 8b OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER Contract No. DAMD17-85-C-5133
8c ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10 SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO: N/A; PROJECT NO: N/A; TASK NO: N/A; WORK UNIT ACCESSION NO: N/A

11 TITLE (Include Security Classification)
Phase I Clinical Pharmacology Studies

12 PERSONAL AUTHOR(S)
Paul S. Lietman, M.D., Ph.D.; Brent G. Petty, M.D.; David M. Kornhauser, M.D.

13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Annual Report	FROM 3/9/88 TO 3/8/89	1989 April 21	20

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	RA I, RA V, Drugs, Infectious Diseases, Malaria
--	--		
--	--		

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Description of overall scope of contract

Description of progress under Task Order #2
Description of progress under Task Order #3
Description of progress under Task Order #6
Description of progress under Task Order #7
Description of progress under Task Order #8 and Amendment
Description of progress under Task Order #9
Description of progress under Task Order #10
Description of progress under Task Order #11
Description of progress under Task Order #12

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL
Mrs. Virginia M. Miller	301/663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

AD_____

Phase I Clinical Pharmacology Studies

ANNUAL REPORT

Paul S. Lietman, M.D., Ph.D.
Brent G. Petty, M.D.
David M. Kornhauser, M.D.

April 21, 1989

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Maryland 21701-5012

Contract No. DAMD17-85-C-5133

Division of Clinical Pharmacology
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205

Summary

This report describes the activities of the Division of Clinical Pharmacology of The Johns Hopkins University School of Medicine during the third and final year of Contract No. DAMD17-85-C-5133. Over this period we have worked on five new clinical studies and increased our clinical activities more than six-fold compared to the first two years of the contract. We believe that the increased efficiency of our effort is in large part related to the establishment and refinement of the "administrative task order," providing for effective communication of information and rapid development of protocols in support of the Army's Drug Development Program. We also believe that we have benefited from an additional year of experience dealing with the Army's administrative requirements.

We summarize the work on four different oral formulations of pyridostigmine. We believe that our familiarity with the pharmacokinetics and pharmacodynamics of pyridostigmine has enhanced the validity of our observations. We also describe a study of the safety and tolerance of multiple once-daily doses of WR 6026 in a placebo-controlled, double-blind study. We are convinced that this study design was essential for correctly interpreting symptoms and abnormalities of laboratory tests that would have been impossible without a placebo control group.

We believe that the excellent and efficient studies conducted during the third year of the contract have met the requirements of the Army's drug development program, and recommend that the relationship we have developed be used as a model for future contract work in Phase I clinical pharmacology studies.

Foreword

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

Table of Contents

1. STATEMENT OF THE PROBLEM

The objective of the contract is "to carry out Phase I clinical pharmacology studies (safety, tolerance, and/or pharmacokinetics) in humans." These studies support the U. S. Army Drug Development Program.

2. BACKGROUND

This contract is the result of a solicitation (DAMD17-84-R-0074) issued by the U. S. Army Medical Research Acquisition Agency on September 24, 1984 entitled "Phase I Clinical Pharmacology Studies" and the response to that solicitation by The Johns Hopkins University School of Medicine on October 31, 1984. The contract was signed on behalf of The Johns Hopkins University on May 23, 1985 and on behalf of The U. S. Army Medical Research and Development Command (USAMRDC) on May 24, 1985. The effective date of the contract was June 1, 1985 and the original term of the contract was to May 31, 1986. The term of the contract was extended to September 1, 1986 on May 21, 1986 and to December 31, 1986 on September 29, 1986. At that point the contract officially ceased while officials of the U. S. Army and The Johns Hopkins University School of Medicine negotiated the terms for two additional years of the contract. Those negotiations were successfully concluded such that the second year of the contract began March 9, 1987. The third and final year of the contract began on March 9, 1988 and this annual report reflects the events of the period March 9, 1988 to March 8, 1989.

Under the terms of the contract the Division of Clinical Pharmacology of The Johns Hopkins University School of Medicine agreed to perform the following:

- Support the USAMRDC drug development program through discussions with the Contracting Officer's Representative (COR) for anticipated studies.

- Develop appropriate background information regarding a particular drug to be tested under the contract, and make suggestions about the protocol to be used.

- Respond to clinical pharmacology inquiries pertaining to current or proposed work.

- Design, create and execute clinical protocols using the Task Order system.

3. APPROACH TO THE PROBLEM

The approach to the problem that we have taken involves the provision of carefully conducted Phase I clinical pharmacology studies as specified by the individual Task Orders provided by the Army and, in addition, the development of a collegial relationship between the involved faculty of The Johns Hopkins University School of Medicine and the involved personnel of The U. S. Army Drug Development Program. This relationship fosters the efficient development of studies that address the important issues concerning the evaluation of new compounds for human use. The positive relationship that has emerged over the life of the contract has allowed smooth and prompt exchange of ideas and recommendations for pursuing the questions raised in the development of the new drugs.

4. RESULTS AND DISCUSSION OF RESULTS

The results that have been realized during this period of the contract will be presented with regard to the general aspects of the contract as well as the specific Task Orders that have constituted the scientific work requested by the Army. During this period, work was performed on Task Order #6 (the administrative task order) and on eight other Task Orders, i.e., Task Orders #2, #3, #7, #8, #9, #10, #11 and #12.

4.1 Contract Overview

This section will be presented in a format that follows, in general, the outline of the contract.

4.1.1. Scope of Work

The contract was originally written in a manner that described in broad and non-specific terms the scope of work anticipated by the Army. During the second year of the contract, as well as during the initial nineteen-month period of the contract, the degree of work was less than anticipated

based on the original solicitation and contract. During this third year, however, the amount of work conducted has increased substantially. The total number of Task Orders initiated this year and the number for which the clinical work was completed was more than either of the past years. In terms of bed-days utilized, the total rose from 168 in Year 1 (19 months) and 108 in Year 2 (an average of approximately 9 bed-days per month in both years), to 684 (57 bed-days per month) in Year 3, the period described in this report. Each proposed study has been accepted and the clinical portion of Task Orders #8, #9, #10, #11 and #12 have been completed. The specifics of the studies we worked on this year are summarized below under specific task orders.

4.1.2 Study Population

A population of male volunteers aged 18-35 has been identified and organized in a manner that promotes the efficient selection of appropriate subjects for each study. This pool of available volunteers is continuously updated and expanded. Recruitment and screening of potential volunteers has occurred throughout the period of the contract. Over the period covered by this report, the clinical portion of Task Orders #8, #9, #10, #11 and #12 have been completed. For those studies, 56 healthy volunteers were entered into the studies, 21 were available as back-ups but not used, and 235 volunteers were screened but rejected. More than half of the rejections were due to elevations of creatine kinase above the published "normal" for the laboratory, which we believe is not an accurate normal range for our healthy subject population.

The "Requirements for the Use of Humans," as defined in the contract, have been strictly followed including Institutional Review Board (IRB) approval of each study involving human subjects; provision of an appropriate HHS Form 596 for each study; and adherence to the requirements of "Title 45, Part 46 of the CFR" as specified by the contract. Institutional Review Board approval was in all cases

obtained from both the Joint Committee on Clinical Investigation (JCCI) at Johns Hopkins and the Surgeon General's Human Subject Research Review Board (HSRRB)

4.1.3 Facilities

A clinical test facility has been provided that offers the requisite equipment and supplies as specified in the contract. A laboratory facility has also been provided in adherence to the specifications of the contract.

In addition, a research laboratory facility has been provided in order to provide immediate and accurate erythrocyte acetylcholinesterase levels as required by the Army in the first two years of the contract and for Task Orders #8, #9, #11 and #12. The development of this capability was in close collaboration with Andris Kaminskis of the Analytical Chemistry Branch of the U. S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland.

4.2 Task Order #2

"Bioavailability of Oral Pyridostigmine and Inhibition of Red Blood Cell Acetylcholinesterase by Oral and Intravenous Pyridostigmine."

Over the period covered by this report, we have continued to expand and refine the exhaustive analysis conducted by Dr. Kornhauser of the pharmacokinetics and pharmacodynamics of pyridostigmine in healthy subjects. These efforts have been a result of discussions with Army personnel after their review of draft task reports submitted in September, 1988 and in January, 1989. We believe that these suggestions have been thoughtful and appropriate, ultimately leading to an improved final task report. As of the end of this reporting period (March 8, 1989), we are completing the final portions of the task report, and believe its formal submission is imminent. We anticipate that Task Order #2 will become the foundation for all subsequent pyridostigmine studies developed and conducted here at Hopkins

under Army sponsorship. The extensive analysis of pyridostigmine pharmacokinetics and effects when given intravenously and when given in syrup will be important standards for comparison as various formulations are assessed.

4.3 Task Order #3

"Single-Dose Absorption and Pharmacokinetics of WR 6026 Hydrochloride in Healthy Subjects."

The final task report for Task Order #3 was submitted August 1, 1988. This report also reflected the beneficial discussions between Johns Hopkins personnel and Army personnel, including different approaches of analyzing and presenting the data.

4.4 Task Order #6

"Task Order Management and Administration."

Task Order #6 was issued at the end of the first year of the contract and continues in effect throughout the year covered in this report. This task order was developed in close collaboration between the U. S. Army Drug Development Program and our group. It represents our combined efforts at developing a plan that will enhance the efficiency of interacting to the mutual advantage of both the Army and Johns Hopkins. This task order authorizes the following:

- Design and create clinical protocols.
- Support the USAMRDC drug development program through discussions with the COR for anticipated studies, (which may become future task orders under this contract).
- Develop appropriate background information regarding a particular drug to be tested under the contract, and make suggestions about the protocol to be used.
- Respond to clinical pharmacology inquiries pertaining to current or proposed work.
- Write/draft procotols.

- Travel to WRAIR to accomplish above.

The effort related to protocol development under Task Order #6 concludes upon the completion of each protocol that becomes ready for submission for institutional review. Effort beyond this point is accounted for under a task order specific for the performance of each protocol.

The creation and implementation of this "administrative task order" was of enormous benefit in facilitating (a) the efficient design and implementation of all subsequent task orders, (b) timely discussions and occasional conferences with USAMRDC personnel, (c) the exchange of background information on drugs to be tested, (d) the response to inquiries pertaining to current and proposed work, and (e) the writing of protocols to be conducted. All of these beneficial features produced a more effective relationship to accomplish the goals of the contract.

4.5 Task Order #7

"Pharmacokinetics and Pharmacodynamics of Sustained, Low-Dose, Intravenous Infusions of Pyridostigmine."

This protocol was designed (1) to assess the relationship between plasma concentrations of pyridostigmine and concurrent erythrocyte acetylcholinesterase inhibition before, during and after achievement of a steady state with continuous intravenous infusion of pyridostigmine; (2) to determine whether erythrocyte acetylcholinesterase and the contractile response of the iris to light are affected to the same degree or proportionally by pyridostigmine; and (3) to assess inter-individual variations in the concentration-effect relations described in (1) and (2).

During the period covered by the third year of the contract and summarized in this report, the results of the pyridostigmine plasma and urine concentrations on the twelve subjects in this study were received from Dr. Emil Lin of the University of California at San Francisco. We have initiated the processing of the iris photographs and have worked to determine an

objective and reproducible method of expressing the changes in pupil size. We have also started the analyses of the plasma pyridostigmine pharmacokinetics and the pharmacodynamic relationship between plasma pyridostigmine concentrations and erythrocyte acetylcholinesterase inhibition. While we believe that this study has substantial scientific merit and may help guide individualization of pyridostigmine dosing in the field, we and Col. Brian Schuster, the COR, have felt that it is less of a priority than the assessment of the different formulations of pyridostigmine being developed and studied, which comprise the work of Task Orders #8, #9, #11 and #12. Therefore, we have put our major efforts into the conduct of those studies and deferred the completion of the analysis of the data for Task Order #7.

4.6 Task Order #8

"Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Oral Doses of Sustained-Released Pyridostigmine in Healthy Men."

Task Order #2 demonstrated that 16 mg of pyridostigmine bromide syrup inhibited erythrocyte acetylcholinesterase by 20-40% within one hour after dosing, but that the inhibition fell below 20% five hours after dosing. In an effort to find a formulation that would provided adequate acetylcholinesterase inhibition for a longer period, sustained-release formulations were developed at the University of Iowa.

The clinical portion of Task Order #8 was completed between January 11, 1988 and February 13, 1988. During this period eight subjects were entered and successfully completed the study in accordance with the approved protocol dated September 18, 1987.

Three preparations were administered to each of the eight subjects. Mestinon^{R} syrup, 22 mg, was used as the standard and compared to single tablets of University of Iowa preparation WRA-24-12226S, a "slow" sustained-release tablet, and WRA-23-12196F, a "fast" sustained-release tablet. Relative bioavailability, as measured by the area under the inhibition-time curve, was reduced for both University of Iowa preparations. The

duration of time the inhibition of erythrocyte acetylcholinesterase was greater than 20% was also less than for the University of Iowa preparations than for syrup. WRA-23-12196F had a greater biologic effect using either of these measures than did WRA-24-12226S.

In view of the reduced effect of both University of Iowa preparations compared to syrup, it was decided to dose subjects with two tablets of WRA-23-12196F, the more active preparation, in order to determine whether a greater biologic effect could be obtained by increasing the dose. Thus, on February 26, 1988, Col. Schuster requested that Task Order #8 be amended to "re-dose 4-6 subjects from the study using 44 mg of the fast release Iowa formulation to test the hypothesis that this dose level would give a satisfactory inhibition profile." This request was forwarded to Contract Specialist Maxine Losee on February 26, 1988. On March 8, 1988 The Johns Hopkins University's IRB approved the amendment to Task Order #8. Army IRB approval was received March 29, 1988.

A budget for the amendment to Task Order #8 was sent to Ms. Losee on April 5, 1988 and approved by Contracting Officer Mr. Danny Laspe on April 19, 1988. The clinical portion of the amendment was completed between April 19, 1988 and April 23, 1988. During this period 4 subjects were entered and successfully completed the study.

The four subjects studied in the amendment to Task Order #8 received 44 mg of the "fast release" University of Iowa preparation. These tablets provided peak inhibition of greater than 20% in all four subjects, range 24-31%, mean 28.5%. The duration of time where inhibition was 20% or greater was 2.0-5.33 hours, mean 3.42 hours.

We have continued our analyses of the pharmacokinetics, relative bioavailability and pharmacodynamics of the two University of Iowa formulations, one of which was given in two different doses. The final report is in preparation.

4.7 Task Order #9

"Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Oral Doses of Sustained-Release Pyridostigmine (Duphar) in Healthy Men."

This study was designed to compare the pyridostigmine pharmacokinetics and the extent and duration of erythrocyte acetylcholinesterase inhibition in healthy human subjects after single doses of 45 mg of pyridostigmine bromide syrup and after 45 mg of pyridostigmine in two different sustained-release formulations produced by Duphar.

Task Order #9 was initiated by the USAMRDC on September 22, 1987. On November 5, 1987 a budget was submitted to Ms. Losee's office. This budget was approved by Mr. Laspe on December 11, 1987. Because of delays in the submission of the Investigational New Drug Application (IND) to the FDA, the project was not submitted to The Johns Hopkins University's IRB until March 3, 1988. Approval was received on March 8, 1988. Army IRB approval was received on March 16, 1988.

The first subject was entered into the study on March 27, 1988. The clinical portion of Task Order #9 was completed between March 27, 1988 and April 30, 1988. During this period 8 subjects entered and successfully completed the study in accordance with the approved protocol dated March 21, 1988.

The "slow release" Duphar tablet gave peak erythrocyte acetylcholinesterase inhibition ranging from 16 to 39%, with a mean of 23.4%. Four of the eight subjects failed to reach 20% inhibition. Of the four subjects whose inhibition was greater than 20%, the duration of time over 20% inhibition ranged from 1.0 to 5.33 hours, with a mean of 2.7 hours. The "fast release" Duphar tablet was substantially better in the degree of acetylcholinesterase inhibition achieved. Peak inhibition ranged from 23 to 59%, with a mean of 36.9%. In all eight subjects, inhibition greater than 20% was achieved, with durations above this level ranging from 0.33 to 8.67 hours (mean 4.03 hours). Despite the increased inhibition with the "fast release" tablet, the equivalent dosage of

syrup provided longer inhibition above 20% (range 4.25-9.0 hours, mean 5.99 hours) and led to peak inhibition of 27-56% (mean 48%).

4.8 Task Order #10

"Multiple-Dose Pharmacokinetics, Safety and Tolerance of WR 6026 Hydrochloride in Healthy Subjects."

The objective of this study was to determine the steady state pharmacokinetics, safety and tolerance of multiple (14) once-daily doses of five different dosages of WR 6026, an 8-aminoquinoline compound with promising activity against Leishmania donovani. The study was designed as a placebo-controlled, double-blind, rising-dose study in healthy volunteers.

Task Order #10 was initiated by the USAMRDC on March 3,1988. IRB approvals were granted on March 22, 1988 by the JCCI and on March 31, 1988 by the HSRRB.

A budget for Task Order #10 was submitted to Mr. Laspe by Dr. Paul Lietman on April 29, 1988 and approved May 3, 1988.

The study was initiated by our group on May 15, 1988. The clinical portion of Task Order #10 was completed between May 16, 1988 and December 16, 1988. During this period 32 subjects entered the study in accordance with the approved protocol dated May 3, 1988.

We conducted the study as specified in the protocol for the four subjects at 5 mg and 15 mg per day. One of the subjects in the second group (15 mg WR 6026 per day or placebo) developed a significant elevation of serum triglyceride level, and after consultation with Dr. Schuster the drug was stopped after only 7 of the planned 14 doses. Approximately 30 hours after the last dose, this subject had what from the description of the nurses and covering intern sounded like a grand mal seizure. Dr. Schuster was notified and authorized an extensive neurological evaluation. In retrospect, it was not clear whether the subject had had seizures before, though he denied a history of seizures during screening and to our neurology consultant who was asked to evaluate

this subject's case. The neurological work-up was negative, including head computerized tomography, electroencephalogram, and metabolic assessment. A full report of both the seizure and the elevated triglycerides (which returned to normal after the study drug was discontinued) was filed with our IRB, with the Army, and with the FDA. Prior to the release of this subject from the study, the randomization code was broken to allow us to identify for him which compound, drug or placebo, he had taken. He had been randomized to receive drug, and was so informed. We believe that the elevation of triglycerides was related to the drug, but that the seizure probably was not.

Dr. Schuster then requested another group of four subjects be tested at the same dose of 15 mg per day to get a better idea of the propensity of this dose to cause such side effects. None of these second four subjects had any significant problems, so the study was continued to include doses of 30 mg, 45 mg, and 60 mg per day, without serious adverse effects.

After the conclusion of the first four subjects at 60 mg per day, the highest planned dose, an additional eight subjects were entered into the study to receive 60 mg WR 6026 or placebo each day for two weeks. For these eight subjects, however, additional clinical specimens (urine and feces, in addition to blood) were collected to assess the bioavailability, excretion patterns, and absorption characteristics of the drug.

A total of 32 subjects were studied under this protocol, four each at 5 mg, 30 mg, and 45 mg per day (or placebo), 8 subjects at 15 mg (as explained above), and 12 subjects at 60 mg per day (or placebo). The subjects generally tolerated the administration of the test compound (WR 6026) quite well. The most common symptomatic complaint was headache, occurring in six subjects, four of whom were randomized to receive the drug. Four subjects had drug administration discontinued before 14 doses, two because of increased serum triglycerides (after 7 and 10 doses) and two because of increased serum aminotransferases (after 5 and 11 doses). Regarding both abnormalities, one subject was randomized to receive drug and one to receive placebo. In one of the two cases of elevated triglycerides,

leading to discontinuation of the drug after 10 doses, the liver function tests had also started rising and reached a significant level 8 days after drug discontinuation. This was the volunteer who had been randomized to the placebo group. There were 9 other volunteers with less remarkable elevations of serum aminotransferases not requiring discontinuation of the study drug. Of these 9 subjects, 4 were randomized to receive drug and 5 to receive placebo. In all cases the aminotransferases returned to normal after stopping the test compound. There was no significant difference between the drug and placebo groups in the incidence of these adverse effects. These observations regarding symptoms, increased triglycerides, and increased liver function tests clearly demonstrate the benefit of having a placebo group included in Phase I safety and tolerance studies.

The most reliable laboratory correlate of randomization to the drug arm was an increased methemoglobin above the normal range, present in all subjects receiving WR 6026 at doses of 60 mg per day, and one of two at both 30 and 45 mg per day.

The last plasma samples from the subjects entered in this study were sent to Dr. Emil Lin of the University of California at San Francisco on October 24, 1988 for assay of WR 6026 levels. No results were received as of March 8, 1989. At the end of this reporting period, the urine and stool specimens were awaiting pick-up by personnel at the Division of Experimental Therapeutics at Walter Reed, delayed somewhat until a freezer malfunction could be corrected.

4.9 Task Order #11

"Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Oral Doses of Pyridostigmine Administered by an Osmotic-Delivery Module (Osmet^{R}) Compared to Pyridostigmine Syrup in Healthy Men."

The objective of this study was to determine the degree and duration of erythrocyte acetylcholinesterase inhibition and the associated plasma pyridostigmine concentrations after administration of a commercial pyridostigmine

syrup and after pyridostigmine administered in an osmotic-release drug delivery system (Osmet^{R}) intended to release a constant amount of pyridostigmine over 24 hours.

This task order was initiated by the USAMRDC on April 19, 1988. The proposal was sent to the Johns Hopkins IRB on May 9, 1988. A budget was submitted to Ms. Losee during May, 1988. This budget was approved by Mr. Laspe on May 20, 1988. There followed a prolonged period of discussion and deliberation between the Osmet^{R} manufacturer and the FDA regarding whether the Osmet^{R} constituted a device or a formulation. The FDA ultimately determined that it should be considered a formulation. In late November, 1988, we learned of this decision and of some minor changes suggested in the protocol and consent form by the FDA. These changes were incorporated into the proposal, and final IRB approvals were granted on December 21, 1988 by the JCCI and on December 27, 1988 by the HSRRB.

The study was initiated on January 9, 1989. The first subject was enrolled into the study on January 9, 1989. The clinical portion of Task Order #11 was completed between January 9, 1989 and February 3, 1989. During this period 8 subjects were entered and successfully completed the study in accordance with the approved protocol dated April 8, 1988.

Because of the possibility of prolonged acetylcholinesterase inhibition from the osmotic delivery of a steady, small amount of pyridostigmine, the design of this protocol included hourly measurement of erythrocyte acetylcholinesterase up to 28 hours after dosing if the inhibition had not returned to less than 5% for 2 consecutive hours. Therefore, on each dosing day we arranged for a laboratory technician and a phlebotomist to obtain and process these required specimens through the 28-hour period.

The Osmet^{R} capsules were prepared at our facility by Dr. Craig Canfield of Pharmaceutical Systems Incorporated. The protocol called for a dose of 141 mg in the Osmet^{R}. However, during the preparation of the initial four doses, a lower dose was placed in each Osmet^{R}. The degree of erythrocyte acetylcholinesterase inhibition was disappointingly low. The peak inhibition ranged

from 11.2 to 20.7%, with a mean peak of 14.8%. For the next four doses, a larger amount (approximately the dose originally scheduled in the protocol and approved by the IRBs) was given. While there was some increase in the magnitude of inhibition of erythrocyte acetylcholinesterase, both the maximal inhibition and the duration of inhibition remained low. The peak inhibition ranged from 15.7 to 28.6%, with a mean of 21.6%. The duration of time with 20% inhibition or more was 0.5 and 1.5 hours in the two subjects whose inhibition exceeded 20%.

Plasma samples from the 8 subjects entered in the study were sent to Dr. Emil Lin of the University of California at San Francisco for a determination of the pyridostigmine plasma and urine concentrations. No reports were received as of March 8, 1989.

4.10 Task Order #12

"Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Oral Doses of a Commercial Formulation of Sustained-Release Pyridostigmine in Healthy Men."

This study was designed to evaluate the pyridostigmine pharmacokinetics and the extent and duration of erythrocyte acetylcholinesterase inhibition in healthy human subjects after single doses of 90 mg and 180 mg of sustained-release pyridostigmine.

Task Order #12 was initiated by the USAMRDC on October 24, 1988. Institutional review board approvals were received on November 30, 1988 from the JCCI on December 6, 1988 from the HSRRB.

A budget for Task Order #12 was submitted to Ms. Losee on November 8, 1988 by Dr. Lietman and approved on December 5, 1988.

The study was initiated by Johns Hopkins on December 5, 1988. The first subject was entered into the study on December 12, 1988. The clinical portion of Task Order #12 was completed between December 12, 1988 and December 23, 1988. During this period four subjects entered and completed the study in accordance with the approved protocol dated October 13, 1988.

The results of the erythrocyte acetylcholinesterase assay are summarized as follows. Four healthy men received a 90 mg dose of the commercial formulation of sustained-release pyridostigmine. Two of these four subjects achieved maximal inhibition of 57% and 52% at 1.67 hours, while the maximal inhibition in the other two was 38% at 2.0 hours and 44% at 1.67 hours. As a result of inhibition greater than 50% in two subjects, we did not give the planned 180 mg dose to these two subjects, as specified in the protocol. The duration of erythrocyte acetylcholinesterase inhibition greater than 20% in these four subjects with 90 mg was 6 hours, 3 hours, 11.5 hours and 5.25 hours (mean 6.44 hours).

The two subjects who had erythrocyte acetylcholinesterase inhibition less than 50% with the 90 mg dose were subsequently dosed with 180 mg of the commercial formulation of sustained-release pyridostigmine. In each case the maximal inhibition achieved was 62%. This was achieved at 1.67 hours in one subject and at 2.5 hours in the other. Inhibition of greater than 20% was sustained for 9.5 hours in one subject and 11.5 hours in the other.

Samples from the four subjects entered in the study were sent to Dr. Emil Lin of the University of California at San Francisco on January 17, 1989 for a determination of plasma pyridostigmine levels. No results were received as of March 9, 1989.

5. CONCLUSIONS

We believe that this contract has met the needs of the U. S. Army Drug Development Program as specified in the contract. The Phase I clinical pharmacology studies that were conducted during this third year of the contract, as the amendment to Task Order #8 plus Task Orders #9, #10, #11 and #12, were performed efficiently and constitute excellent studies. Task Orders #2, #3, #7 and #8 have also received attention during the course of this third contract year. An excellent working relationship has been developed between our group and the U. S. Army Drug Development Program.

6. RECOMMENDATIONS

We recommend that the working relationship that we have developed over the three years of this contract with the Army be used as a model for future contract work in the area of Phase I clinical pharmacology studies. Our experiences have led to the development of an excellent working relationship with the U. S. Army Drug Development Program and to the creation, implementation, and efficient completion of scientifically sound studies that have provided clear and decisive answers to the questions posed by this program.

DISTRIBUTION LIST

1 copy: Director, Walter Reed Army Institute of Research
ATTN: SGRD-UWI-F/COL Brian Schuster
Washington, D.C. 20307-5100

4 copies: Director, Walter Reed Army Institute of Research
ATTN: SGRD-UWI-D
Washington, D.C. 20307-5100

1 copy: Commander
U. S. Army Materiel Development Activity
ATTN: SGRD-UMP-T
Fort Detrick
Frederick, Maryland 21701-5009

2 copies: Administrator
Defense Technical Information Center
ATTN: DTIC-DDAC
Cameron Station
Alexandria, Virginia 22314-6145

1 copy: Commander
U. S. Army Medical Research and Development Command
ATTN: SGRD-RMI-S
Fort Detrick
Frederick, Maryland 21701-5012

1 copy: Commander
U. S. Army Medical Research Acquisition Activity
ATTN: SGRD-RMA-RCD/Maxine Losee
Fort Detrick
Frederick, Maryland 21701-5014